heterocyclic, aryl and heteroaryl group to form a bi- or tri-fused ring system and further wherein said heterocyclic group and each of said ring structures are optionally substituted with 1 to 3 substituents selected from the group consisting of hydrogen, halogen, hydroxy, alkoxy, substituted alkoxy, amino, alkylamino, substituted alkylamino, dialkylamino, substituted dialkylamino, acylamino, aminoacyl, substituted acylamino, N-acyl-N-alkylamino, substituted N-acyl-N-alkylamino, alkylene dioxy, (alkylsulfonyl)amino, substituted (alkylsulfonyl)amino, N-(alkylsulfonyl)-N-alkylamino, substituted N-(alkylsulfonyl)-N-alkylamino, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, cycloalkenyl, substituted cycloalkenyl, alkynyl, substituted alkynyl, cyano, acyl, substituted acyl, carboxy, substituted carboxy, nitro, thiol, alkylthio, substituted alkylthio, alkylsulfoxy. substituted alkylsulfoxy, alkylsulfonyl, substituted alkylsulfonyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl;--

A1

Please amend the paragraph bridging pages 16-17 to read as follows:

--(a) a group wherein W, together with -C(=Z)NR^2- where Z is -O-, forms an unsaturated heterocyclic group containing 3 or 4 carbon atoms and 0 or 1 additional nitrogen atom and further wherein the unsaturated heterocyclic group is optionally substituted, in addition to the R^2 group, with 1 or 2 substituents selected from the group consisting of alkyl, alkoxy, substituted alkoxy, alkenyloxy, substituted alkenyloxy, halo, hydroxy, mono or dialkylamino. Preferably B is 2-pyridone, (e.g., 2-pyridon-3-yl, 2-pyridon-4-yl, etc.,) or 6-pyrimidone (e.g., 6-pyrimidon-5-yl, etc.,) that is optionally substituted, in addition to the R^2 group with 1 or 2 substituents selected from the group consisting of alkyl, alkoxy, substituted alkoxy, alkenyloxy, substituted alkenyloxy, halo, hydroxy, mono or dialkylamino, more preferably methyl, ethyl, propyl, methoxy, ethoxy, propoxy, butoxy, allyloxy, butenyloxy (wherein the methyl, ethyl, propyl, butyl, and allyl group in said methoxy, ethoxy, propoxy, butoxy, allyloxy, butenyloxy may be optionally substituted with 1 to 3 substituents selected from the group consisting of hydroxy, alkoxy, thiol, alkylthio, alkylsulfoxide, alkylsulfone, halo, alkylamino, dialkylamino, amino,

A2

A2

aminoacyl, preferably, hydroxy, methoxy, ethoxy, methylthio, methylsulfane, methylsulfone, fluoro, methylamino, dimethylamino, amino, and acetylamino), chloro, bromo, hydroxy, methylamino, or dimethylamino. More preferably in the above rings R^2 is alkyl, preferably methyl; or--

Please amend the paragraph bridging pages 23-24 to read as follows:

--B is a group wherein W, together with $-C(=Z)NR^2-$, forms a saturated or unsaturated heterocyclic group containing 2 to 5 carbon atoms and 0 to 4 additional heteroatoms selected from the group consisting of nitrogen, oxygen, and $-SO_n-$ (where n is 0 to 2) wherein said saturated or unsaturated heterocyclic group is optionally fused with one or two ring(s) structures selected from the group consisting of cycloalkyl, cycloalkenyl, heterocyclic, aryl and heteroaryl group to form a bi- or tri-fused ring system and further

A3

wherein said heterocyclic group and each of such ring structures are optionally substituted with 1 to 3 substituents selected from the group consisting of hydrogen, halogen, hydroxy, alkoxy, substituted alkoxy, acyloxy, substituted acyloxy, amino, alkylamino, substituted alkylamino, dialkylamino, substituted dialkylamino, acylamino, substituted acylamino, N-acyl-N-alkylamino, substituted N-acyl-N-alkylamino, alkylene dioxy, (alkylsulfonyl)amino, substituted (alkylsulfonyl)amino, N-(alkylsulfonyl)-N-alkylamino, substituted N-(alkylsulfonyl)-N-alkylamino, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, cycloalkenyl, substituted cycloalkenyl, alkynyl, substituted alkynyl, cyano, acyl, substituted acyl, carboxy, substituted carboxy, nitro, thiol, alkylthio, substituted alkylthio, alkylsulfoxy, substituted alkylsulfoxy, alkylsulfonyl, substituted alkylsulfonyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl; and

enantiomers, diastereomers, and pharmaceutically acceptable salts thereof.--

Please amend the paragraph at page 24 beginning at line 8 to read as follows:

--In the above compounds III(a-e), B is either:

(a) a group wherein W, together with $-C(=Z)NR^2-$ where Z is -O-, forms an unsaturated heterocyclic group containing 2 to 4 carbon atoms and 0 to 2 additional nitrogen atoms and further wherein the unsaturated heterocyclic group is optionally substituted, in addition to the R^2 group, with 1 or 2 substituents selected from the group consisting of alkyl, alkoxy, substituted alkoxy, alkenyloxy, substituted alkenyloxy, halo, hydroxy, mono or dialkylamino. Preferably B is 2-pyridone, (e.g., 2-pyridon-3-yl, 2-pyridon-4-yl, etc.,) or 6-pyrimidone (e.g., 6-pyrimidon-5-yl, etc.,) that is optionally substituted, in addition to the R^2 group, with 1 or 2 substituents selected from the group consisting of alkyl, akoxy, substituted alkoxy, alkenyloxy, substituted alkenyloxy, halo, hydroxy, mono or dialkylamino, preferably methyl, ethyl, propyl, methoxy, ethoxy, propoxy, butoxy, allyloxy, butenyloxy (wherein the methyl, ethyl, propyl, butyl, and allyl group in said methoxy, ethoxy, propoxy, butoxy, allyloxy, butenyloxy may be optionally substituted with 1 to 3 substituents selected from the group consisting of hydroxy, alkoxy, thiol, alkylthio, alkylsulfoxide, alkylsulfone, halo, alkylamino, dialkylamino, amino, aminoacyl, preferably, hydroxy, ethoxy, methoxy, methylthio, methylsulfane, methylsulfone, fluoro, methylamino, dimethylamino, amino, and acetylamino), chloro, bromo, hydroxy, methylamino, or dimethylamino. More preferably in the above rings R^2 is alkyl, preferably methyl; or--

A4

Please amend the paragraph at page 29 starting at line 15 to read as follows:

--X is hydroxyl;--

A5

Please amend the paragraph bridging pages 30-31 to read as follows:

--The compounds and pharmaceutical compositions of this invention are useful for treating disease conditions mediated by VLA-4 or leukocyte adhesion. Such disease conditions include by way of example, asthma, Alzheimer's disease, atherosclerosis, AIDS dementia, diabetes (including acute juvenile onset diabetes), inflammatory bowel disease

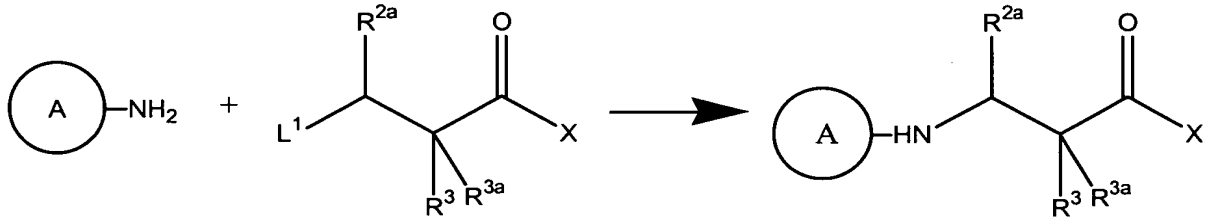
A6

(including ulcerative colitis and Crohn's disease), multiple sclerosis, rheumatoid arthritis, tissue transplantation, tumor metastasis, meningitis, encephalitis, stroke, and other cerebral traumas, nephritis, retinitis, atopic dermatitis, psoriasis, myocardial ischemia and acute leukocyte-mediated lung injury such as that which occurs in adult respiratory distress syndrome.--

Please amend the paragraph bridging pages 65-66 to read as follows:

--In another preferred embodiment, compounds of this invention may be prepared by displacement of a leaving group as shown in scheme 2:

Scheme 2



7 **8** **I**

where R^{2a}, R^3, R^{3a} and X are as defined herein; A is heteroaryl, substituted heteroaryl, heterocyclic or substituted heterocyclic containing two nitrogen atoms in the heteroaryl or heterocyclic ring; and L^1 is a leaving group, such as chloro, bromo, iodo, sulfonate ester and the like.--

Please amend the paragraph bridging pages 68-69 to read as follows:

--A comound of formula (I) can also be prepared by first reacting **10** wherein A is as defined herein, X^3 is halogen, such as chloro, bromo or iodo (preferably iodo) with a 3-

aminopropionic acid derivative of formula **13** wherein R^y is a suitable group that can be converted to a R^{2a} group which is defined in the Summary of the Invention. Initially, reaction of a compound of formula **10** with a compound of formula **13** under the reaction conditions described above provides an intermediate of formula **14** which is then converted to a compound of formula **(I)**. It will be well recognized by those skilled in the art that the choice of the R^y substituent will depend on the type of R^{2a} group desired in compound **(I)**. For example, if a compound of formula **(I)** where R^{2a} is $-Ar^1-R^9$ wherein Ar^1 is phenyl and R^9 is a carbamoxy group is desired, then it can be prepared by first coupling **10** with a (R)-3-amino-3-(4-(*tert*-butyldimethyl-siloxy)phenyl)propanoic acid ethyl ester to give N-substituted-(4-(*tert*-butyldimethyl-siloxy)phenyl)propanoic acid ethyl ester which upon deprotection of the hydroxy group provides N-substituted-(4- hydroxyphenyl)propanoic acid ethyl ester. N-Substituted-(4-hydroxyphenyl)propanoic acid ethyl ester can then be contacted with about 1.0 to about 1.2 equivalents of a chloroformate in an inert diluent, such as dichloromethane, at a temperature ranging from -25 °C to about 0°C for about 0.5 to about 2.0 hours. Treatment of the resulting carbonate with an excess, preferably about 2 to about 5 equivalents, of a trialkylamine, such as triethylamine, for about 0.5 to about 2.0 hours, followed by about 1.0 to about 1.5 equivalents of a primary or secondary amine provides the carbamate. Examples of amines suitable for use in this reaction include, but are not limited to, piperazine, 1-methylpiperazine, 1-acetylpiperazine, morpholine, thiomorpholine, pyrrolidine, piperidine and the like.--

A8

Please amend the paragraph bridging pages 75-76 to read as follows:

--Alternatively, a hydroxyl group present on a substituent of a compound of formula I-IV or an intermediate thereof can be O-alkylated using the Mitsunobu reaction. In this reaction, an alcohol, such as 3-(N,N-dimethylamino)-1-propanol, is reacted with about 1.0 to about 1.3 equivalents of triphenylphosphine and about 1.0 to about 1.3 equivalents of diethyl azodicarboxylate in an inert diluent, such as tetrahydrofuran, at a temperature ranging from about -10°C to about 5°C for about 0.25 to about 1 hour. About 1.0 to about

A9

A9 1.3 equivalents of a hydroxy compound, such as N-*tert*-butyltyrosine methyl ester, is then added and the reaction mixture is stirred at a temperature of about 0°C to about 30°C for about 2 to about 48 hours to provide the O-alkylated product.--

Please amend the paragraph at page 84 starting at line 30 to read as follows:

--The active ingredient, starch and cellulose are passed through a No. 20 mesh U.S. sieve and mixed thoroughly. The solution of polyvinyl-pyrrolidone is mixed with the A10 resultant powders, which are then passed through a No. 16 mesh U.S. sieve. The granules so produced are dried at 50°C to 60°C and passed through a No. 16 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate, and talc, previously passed through a No. 30 mesh U.S. sieve, are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets each weighing 120 mg.--